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13. ABSTRACT *(Maximum 200 words)*

We have performed a study of the effects of hemorrhagic shock and resuscitation on isolated heart function of guinea pigs. In vivo hemodynamics were monitored during hemorrhage, shock and resuscitation and then intrinsic function of the heart was assessed. Three time periods were studied - 1, 2 or 3 hours of shock. In some animals shock lasted for 1 hour and then guinea pigs were resuscitated with whole blood or dextran 70,000 MW (same volume as the blood that was removed). The data collected from the isolated heart indicated that hemorrhagic shock lasting 1, 2 or 3 hours by itself did not cause major dysfunction of the heart. The only change in heart function that seems to occur was in the 3 hour shock group in which the left ventricular compliance was slightly depressed. In animals that had been resuscitated with whole blood or with 6% dextran, ventricular performance was depressed compared to control hearts and compared to hearts from animals in hemorrhagic shock suggesting that reperfusion contributed significantly to myocardial dysfunction resulting from hemorrhagic shock. We have also demonstrated that resuscitation with Ringers' lactate improves cardiovascular status to the same extent as does dextran. Giving four times the shed blood volume vs a volume equal to the shed volume, however, made little difference in the recovery noted. Finally, we have determined that alcohol, given 30 min prior to the hemorrhage, impairs the cardiovascular and respiratory compensation for severe blood loss and results in greater mortality.

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ANNUAL PROGRESS REPORT

GRANT TITLE: Myocardial Dysfunction Contributes to Irreversible Hemorrhagic Shock

PRINCIPAL INVESTIGATOR: Kathleen H. McDonough (email kmcdon@lsuhsc.edu)

INSTITUTION: Louisiana State University Medical Center

GRANT NUMBER: N00014-96-1-1274

AWARD PERIOD: September 1, 1996 - September 30, 2000

REPORTING PERIOD: September 1, 1996 - September 30, 2000

OBJECTIVE: To investigate the effects of hemorrhagic shock on the myocardium and to determine if myocardial dysfunction contributes to irreversibility of hemorrhagic shock.

APPROACH: Guinea pigs are anesthetized and polyethylene catheters are placed in the carotid artery for measurement of blood pressure and sampling of arterial blood and into the right atrium via the jugular vein for delivery of resuscitation fluids and anesthesia for sacrifice of the animals. In some animals a thermistor probe is placed in the other carotid artery for measurement of cardiac output by thermodilution. When the instrumented guinea pigs begin gaining weight (approximately 2 days after surgery), they are weighed and after control hemodynamics have been measured and an arterial blood sample taken, blood is removed at a rate of 1 ml/min. The percent of the blood volume that is removed varies depending upon the protocol to be followed. In all protocols however, blood volume is assumed to be 6% of the body weight as measured previously in this laboratory. Blood pressure, heart rate, hematocrit and blood glucose and lactate are measured at regular intervals. Animals are maintained in shock for various periods of time from 1 to 3 hr and in some experiments animals are resuscitated with their own blood or with a commonly used resuscitation fluid. Critical features of this protocol include the fact that the animals are allowed to recover from the initial surgery until they begin gaining body weight (and thus have restored their body fluid volumes) and that hemorrhage occurs in the conscious animal. After various periods of shock and/or resuscitation and after the final measurements of hemodynamics and blood chemistry have been made, animals are anesthetized and their hearts are removed for analysis of intrinsic myocardial dysfunction. The isovolumic beating heart preparation is used so that systolic and diastolic performance can be assessed and hearts are studied under the physiologic stresses of increasing balloon volume or preload and increasing beating rate. Both stresses can be used to unmask deficits in myocardial contractile reserve. In some studies the response to changes in coronary flow have been assessed and the sensitivity of hearts from shocked animals to ischemia and reperfusion injury has been assessed.

ACCOMPLISHMENTS: Our earliest studies used a hemorrhage protocol in which 50% of the animal's blood was removed and animals were maintained in that shock state for 1, 2 or 3 hr at which time hearts were removed for assessment of myocardial performance. In those studies we demonstrated that ventricular performance was not altered by 1 or 2 hr shock by itself but by 3 hr there was an indication of a decrease in myocardial compliance. In addition left ventricular developed pressure (LVDP), as a function of left ventricular end diastolic pressure, was depressed compared to control in hearts removed from animals after 3 hr of shock. Thus hemorrhagic shock induced by removal of 50% of the blood volume by itself did not result in changes in intrinsic myocardial function until shock had lasted for 3 hr. These studies were published in SHOCK 11:205-210, 1999.

In order to determine if resuscitation caused injury separate from the hemorrhage induced injury, we have completed studies in which animals were bled and maintained in shock for 1 hr and were then resuscitated. Some of the animals were resuscitated with their own blood and some were resuscitated with dextran (6%), a volume equal to the shed blood, after one hr of shock. Heart function, as well as in vivo hemodynamics, was assessed at 1 hr after resuscitation and 24 hr after resuscitation. Interestingly, animals receiving blood resuscitation after 1 hr shock demonstrated depression of myocardial function to a greater extent than did hearts from animals that received dextran resuscitation. This dysfunction was due to systolic rather than diastolic depression. Hearts seemed to recover by 24 hr although there was residual dysfunction in the hearts of the blood-resuscitated animals. These results suggested that myocardial dysfunction can result from resuscitation or "reperfusion" injury similar to that which occurs after ischemia. This type of injury that occurs early after ischemia and reperfusion but is reversed by 24 hr has been termed "stunning" and is thought to be due to oxygen free radicals, calcium overload and insufficient myocardial high-energy phosphate levels. These studies have been published in the Journal of Trauma 48:1122-1127, 2000, "Effects of Blood Resuscitation vs. Dextran Resuscitation after Hemorrhage on Intrinsic Myocardial Function", KH McDonough, ME Giaimo, M Quinn and HI Miller.

We have also studied the effects of fluid resuscitation using the crystalloid lactate Ringers. We hypothesized that resuscitation with lactate Ringers solution administered at 4 times the volume of shed blood could result in a volume overload on the myocardium and therefore exacerbate resuscitation-induced injury to the heart. Therefore we compared the effects of resuscitation with Lactate Ringer's at the same volume as the shed volume with Lactate Ringers given at 4 times the shed volume on hemodynamic and cardiac recovery from hemorrhagic shock. In these studies, 70% of the estimated blood volume was removed and after the 2 hr shock period, animals were resuscitated with either 1 times the shed blood volume (1x) or 4 times the shed blood volume (4x) with Lactate Ringers solution.

				-------60' R-----		-----24 h R-----		---48 h R--	
	Pre	O'HS	120'HS	1x	4x	1x	4x	1x	4x
MABP	76± 2	34± 3	45± 2	46± 2 *	53± 2	60± 3	58± 2	60± 2	66± 2
HR	307 ±15	326± 10	332± 7	315± 12	319± 9	344 ±9	310± 2	270± 1	340± 14
Lactate	10± 1	82± 7	60± 9	32± 5	40± 7	14± 1	20± 4	14± 3	20± 5
Glucose	97± 3	240± 12	144± 1	112± 8	99± 6	136± 2	129± 6	138± 4	125± 18
Hct	41± 1	27± 1	21± 1	18± 0 *	16± 0	14± 1	14± 0	16± 1	15± 1

MABP = mean arterial blood pressure, mmHg; HR = heart rate, beats per min; Hct = hematocrit, %; Lactate, mg/dl; glucose, mg/dl; HS – hemorrhagic shock (begins at the time at which 70% of the blood volume has been removed); R = resuscitation.

These data suggested that the only benefit derived from the 4x resuscitation was at 60 min R (at the end of the 4x resuscitation) and that this benefit was not prolonged. In fact survival to 48 hr was not significantly different in the two groups again suggesting that the greater volume of resuscitation had no beneficial or detrimental effects on recovery from 2 hr HS.

We have recently begun measuring respiratory parameters during shock and resuscitation. We have found that during shock pO2 increases and pCO2 decreases probably in response to stimulation of the peripheral arterial chemoreceptor by the lactic acidemia (lactate levels increase 4 fold during shock whereas glucose levels increase a little over 2 fold). During shock, O2 consumption and CO2 production decrease and the respiratory exchange ratio progressively decreases from .96 before bleeding to .81 at 1 hr resuscitation. The RER is back to control levels by 24 hr resuscitation. We are developing this model in order to study the effects of metabolic support of animals during hemorrhagic shock and resuscitation. These studies have also included the response to hemorrhagic shock when alcohol, at the level considered legally intoxicated, is present. Alcohol seriously impairs the compensation by the cardiovascular and respiratory systems leading to greater lactate accumulation, lower arterial pH and greater mortality in the animals administered alcohol 30 min prior to the bleeding procedure. This study has been submitted to the J. Trauma recently.

SIGNIFICANCE: These studies indicate that a relatively prolonged period of shock can be tolerated with minimal cardiac dysfunction. However, resuscitation, while resulting in recovery of hemodynamic status can result in reversible stunning of the myocardium. The consequences of this stunning by itself may not be life threatening but in the human condition in which coronary artery disease can compromise coronary reserve, stunning can result in a more prolonged and more severe compromise of myocardial function. Composition of resuscitation fluid can be modified to potentially prevent blood-induced injury if indeed that injury is due to activation of neutrophils.

WORK PLAN: Funding ended September 30, 2000. Data collected from this support will be used to apply for funding from the NIH

PUBLICATIONS, ABSTRACTS, TECHNICAL REPORTS, PATENTS, AND AWARDS:

1) Chamulitrat, W, HI Miller, KH McDonough. Priming of Peyer's Patch Lymphoid Cells by Hemorrhagic Shock and Resuscitation to Produce Superoxide Radical. SHOCK 11:136-142, 1999.
2) McDonough, KH, M Giaimo, M Quinn, HI Miller. Intrinsic Myocardial Function in Hemorrhagic Shock. SHOCK 11:205-210, 1999.
3) HI Miller, ME Giaimo, M Quinn and K.H. McDonough. Effects of different resuscitation volumes on recovery from hemorrhagic shock. Exp. Biol 1999.
4) McDonough KH, ME Giaimo, M Quinn, HI Miller. Effects of Blood Resuscitation vs. Dextran Resuscitation on Intrinsic Myocardial Function. J. Trauma 48:1122-1127, 2000.
5) McDonough KH. ME Giaimo, HI Miller. Low dose alcohol alters the cardiovascular, metabolic and respiratory compensation for severe blood loss. Submitted – J Trauma

PROJECT HIGHLIGHT

1 June 1999 – 30 September 2000

NAME: Kathleen H. McDonough

INSTITUTION: Louisiana State University Medical Center

PROJECT HIGHLIGHT

Our most significant result has been the demonstration that in the conscious guinea pig, severe blood loss can be sustained without loss of myocardial reserve until approximately 3 hr of shock (blood loss of approximately 50% of the animal's blood volume). At time periods less than 3 hr of shock, resuscitation with blood or dextran or Ringer's lactate results in myocardial depression as assessed in the isolated heart preparation in which ventricular pressure development can be assessed and heart function can be varied by pacing the heart at different rates, altering coronary flow or changing ventricular diastolic volume. The depression is reversible by 24 hr after resuscitation had been administered. This suggests that the myocardium is "stunned", which in the ischemia reperfusion literature is the term applied to myocardial dysfunction after ischemia and reperfusion that is reversed by 24 hr recovery. The implications for resuscitation in the human are serious since in human hemorrhage and resuscitation, coronary artery disease which compromises myocardial perfusion, is an unknown factor. As humans age, the degree of coronary artery disease increases in a non-uniform and non-universal manner such that the degree of disease is unknown unless invasive procedures are used to measure coronary flow. Thus the status of the coronary circulation in resuscitated patients can lead to serious complications to a relatively innocuous shock period when resuscitation may exacerbate myocardial damage.

MAJOR PROBLEMS: The original start date for this grant was September 1, 1996. However, funding was not available to the investigators until February 1997. Technical help was not hired until June, 1997 and that individual resigned his position in December, 1997 to return to school. Therefore during the first year, less research was performed than originally predicted and we were granted a no cost extension until September 30, 2000. The model has

been developed and is a significantly improved model because animals are allowed to recover from the initial surgery and gain weight and during the hemorrhage and resuscitation are conscious. Four publications have been produced with two more manuscripts in preparation. In addition, substantial information has been accumulated that will form the basis for applications for funding from the NIH.

POTENTIAL PATENTABLE INVENTIONS: None

ANNUAL REPORT QUESTIONNAIRE

1 June 1999 – 30 September 2000

GRANT TITLE: Myocardial Dysfunction Contributes to Irreversible Hemorrhagic Shock

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GRANT NUMBER: N00014-96-1-1274

AWARD PERIOD: September 1, 1996 - September 30, 2000

ONR PROGRAM OFFICER: Jeannine A. Majde, Ph.D.

TECHNOLOGY TRANSFER: None

ONR DATABASE STATISTICS:

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Number of Patents Issued: 0

Number of Patents Pending: 0

Number of Presentations: 1

Number of Degrees Granted: 0

Number of Principal Investigators (PI):/co-PI 3
PI/co-PI Women 2
PI/co-PI Minority 0

Number of Associates Investigators (AI) (Total) 3
AI Women 2
AI Minority 0

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Number of Doctoral Students Supported (Total): 0

Number of Masters Students Supported (Total): 0

Number of Undergraduate Students Supported (Total): 2
Undergraduate Women: 1
Undergraduate Minority:

List Other Sponsored Work: None

List Foreign Collaborations: None